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With international search report.

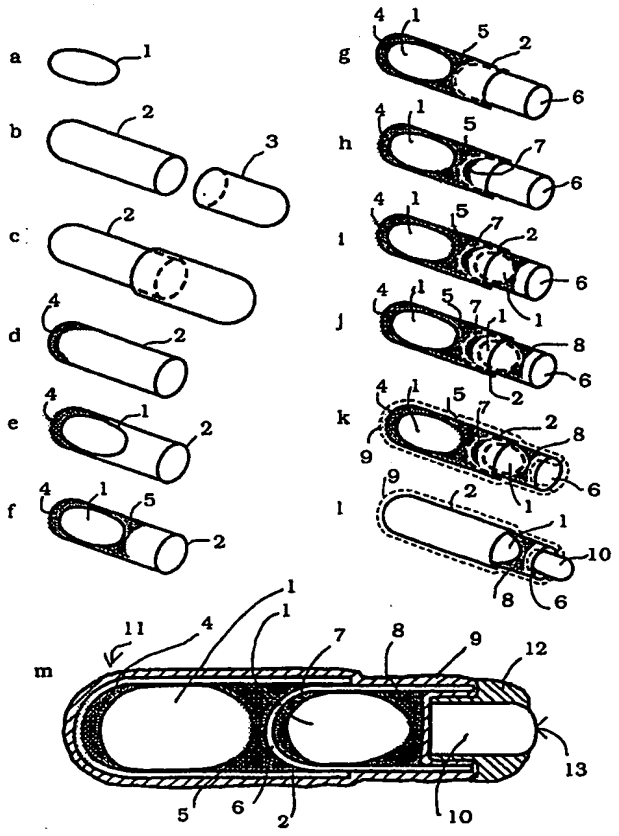
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

In English translation (filed in Swedish).

(54) Title: DIAGNOSTIC METHOD AND DIAGNOSTIC MEANS USED IN CARRYING OUT SAID METHOD

(57) Abstract

The present invention relates to a diagnostic method used to indicate the migration of a medicament through the digestive apparatus and its resorption during this migration, with the use of a negative MRI–contrast agent, e.g. Abdoscan, and a positive contrast substance, introduced into gelatin capsules. In accordance to the invention said gelatin capsules are arranged as inner capsules in a common outer capsule, which is provided with barium sulpate in such an amount, that the specific gravity of the filled outer capsule is higher than the specific gravity of the contents of the stomach, so that the capsule will be able to sink through the contents of the stomach and reach the small intestine without a substantial time–delay. The invention also relates to a diagnostic means used to carry out the diagnostic method.



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substance and the signal-negative shell respectively, which latter consists of paraffin plus barium sulphate.

In the human body there are no structures, which yield such a or a similar signal pattern in MRI, which substantially facilitates the finding of the capsule.

Also, the capsule is now so heavy, that it finds its way by itself to the lower outlet of the stomach.

As regards the dissolution , which is too quick, I have considered using beeswax, which does not melt or is not dissolved at body temperatures. Thus, I have provided the dry gelatin capsule on its outer side with liquid beeswax and have let the wax cool. The capsule is, thanks to the included barium, still sufficiently heavy to sink. However, thanks to the wax it has not even been dissolved, when it reaches the anal opening, which is perfect from the point of view, that it then also is not able to influence the examination of the substance, which is to be examined. Instead of beeswax it is possible to use a layer, which consists of a mixture of solid paraffin (paraffinum solidum) and barium sulphate in order to obtain a protection of the capsule, and at the same time the barium sulphate contributes to the necessary weight.

The substance to be examined is wrapped up in or is mixed with solid paraffin (paraffinum solidum). This solid paraffin portion constitutes the cargo portion itself, i.e. that portion, which is optional and can be united with the trace portion of the capsule. The release/dissolution takes place slowly or at a certain pH-value. It is done by coating the substance to be examined with a pH-sensitive substance. This method has been tested during several decades by the pharmaceutical industry and is used by routine in certain pharmacological preparations. Thus, the method allows a utilization of all this experience, how medicaments are to be mixed with paraffin in order to be released slowly and consequently in a careful way, or put in another way, intentionally during a longer time in order to provide the same medicament concentration during a long time.

Instead of beeswax another non-toxic substance can be used, which melts or dissolves only at higher temperatures than the temperatures of the body, e.g. at 40 - 50oC, and which at least during a sufficiently long time is able to resist the liquids in the body without dissolving in the wrong intestinal section and with that effect respectively, that it is dissolved in the proper intestinal section and also during a long time.

My tests have shown, that it is possible to indicate the capsule all the way from the stomach and through the entire small intestine and also in the colon

in its section close to the anal opening.

The present invention is not limited to what has been stated above, which only is to be considered a non-limiting embodiment, which can be modified and supplemented in an arbitrary fashion within the scope of the inventive idea and the following claims respectively.

Instead of paraffin other substances can be used, e.g. waxes plus non-toxic substances heavier than water instead of barium sulphate.

The substance to be examined can either be included in the outer capsule/the outer shell in the form of a separate capsule (the cargo capsule) or be mixed with the chemically inert substance of the shell.

I have found, that a capsule according to the invention gives such a clear signal picture against the used contrast agent, that despite small amounts of substances remaining in the stomach and the intestines the otherwise mandatory purging before the examination is not required. This results not only in a substantial relief for the patient, who avoids the inconvenience of having at least one day lost due to the purging, but also in another advantage : A purging leads to an increased mobility in the intestines. This increased mobility is a substantial drawback during MRI-examinations, since the picture taking per se takes time (reminding one of the old-fashioned photographing, when it was necessary to stand absolutely still for a long time in order to obtain a sharp picture). However, it is not possible to stop the movements of the intestines by sheer will-power. On the other hand the intestines hold substantially steady, if no purging is used and one keeps fasting from the evening before the examination and then in the morning swallows the contrast agent and the capsule, which provides excellently sharp pictures despite certain small remaining amounts of substances in the stomach/intestines.

None of the other described diagnostic means has, according to what I as a physician know about it, had any substantial medical impact. None of them is said to be used commercially despite the fact, that these means have been known for several decades.

The enclosed drawings show as a non-limiting illustrating embodiment a method of producing a diagnostic means 11 according to the invention. The drawings show in detail:

a) an inner capsule 1, which contains a positive contrast substance ;
b) a lower portion 2 and upper portion 3 of a conventionel outer capsule. In this example only the lower portion is used as an outer capsule ;

c) an otherwise possible outer capsule, which consists of a lower portion + an upper portion ;

d) on the bottom of the lower portion the application of a first dose 4 of a heavy substance, e.g. barium sulphate, possibly barium sulphate and iron oxide ;

e) an inner capsule, inserted in the lower portion, prepared in this way, avoiding air inclusions. Alternatively, it is in this case possible to form a possibly desirable small air inclusion in order to facilitate a vertical positioning of the means in e.g. the stomach ;

f) a second dose 5 of a heavy substance, applied on top of the inserted inner capsule ;

g) a lower portion 6 of a second outer capsule, inserted with forced fit into the first lower portion, air inclusions being avoided ;

h) a third dose 7 of a heavy substance, inserted into the second lower portion ;

i) a second inner capsule , inserted into the second lower portion, prepared in this way ;

j) a fourth dose 8 of a heavy substance, inserted into the second lower portion on top of the second inner capsule ;

k) a thin layer 9 of liquid beeswax , applied to the outside of the construction, obtained in this way, and also to the inside of the from the outside available portion of the second lower portion and to the free outside of said fourth dose 8 ;

l) a cargo portion 10, which consists of or contains a substance, which is to be examined , which substance in a typical case is a drug substance, mixed with paraffin and is inserted into the open end of the second lower portion to fill this and be joined with its outer paraffin portions with the wax, which is still liquid ; and

m) the border area between the wax layer and said paraffin portions, fused together in a way similar to how thermoplastic materials fuse together. In this way some form of alloy or soldering together of adjacent portions is obtained and is it guaranteed in a far-reaching way, that this entire construction is kept together up to the end, i.e. until this means has left the body. In order to facilitate the swallowing of said means a part of the cargo portion , particularly the sides, which are parallel to the lower portions, can be provided with a paraffin layer 12, a soft transition zone between wax layer 9 and cargo portion 10 being obtained. However, the rest of the outer side of the latter, particularly its outer free end 13, is not covered by the paraffin layer, a dissolution, a leaching or the like in relation to present liquids in the body being possible.

The present invention is not limited to the embodiments described above and/or shown in the accompanying drawings but can be modified and supplemented in an arbitrary fashion within the scope of the inventive idea

and the following claims. Thus, barium sulphate and/or iron oxide are only to be regarded as examples. They can of course be replaced with other suitable substances, provided such substances are sufficiently heavy and satisfactorily function as contrasting agents respectively. Also, the term capsule and capsules respectively can be replaced with other forms of enclosing/limiting means, e.g. various forms of coating and/or treatment and filling respectively during a preferably fully automatic production process. By using a powdery substance or substance mixture the inner capsules will not be exposed to moisture. However, in case the material of the inner and outer capsules respectively is resistant to e.g. a water solution, which contains said heavy substance and contrast agent respectively, it is of course possible to use such a solution instead ot a powder.

CLAIMS

1. A diagnostic method to visualize the migration of a medicament through the digestive apparatus and how the medicament is resorbed during this migration by using a negative MRI-contrast agent, e.g. Abdoscan, and a positive contrast and signal substance, filled in one or several capsules made of e.g. gelatin , **c h a r a c t e r i z e d in that** said one or several capsules made of e.g. gelatin are inserted as inner capsules in a common outer capsule, which is provided with a heavy substance, preferably barium sulphate, in such an amount , that the specific gravity of the filled outer capsule is higher than the specific gravity of the contents of the stomach, this capsule being able to sink through the contents in the stomach and reach the small intestine without any substantial time-delay.

2. A diagnostic method according to claim 1, **c h a r a c t e r i z e d in that** iron oxide is inserted into the outer capsule to form a properly contrasting negative near zone in relation to and around the inner capsule and the inner capsules respectively, and/or in that said positive contrast and signal substance is a natural or synthetic organic non-toxic subtance, preferably a deep-sea fish oil and/or in that the dissolution of the outer capsule and possibly also the inner capsule or the inner capsules respectively is delayed or counter-acted, at least during a certain predetermined time, by a coating, known per se, with beeswax and/or another non-toxic substance, which melts or is dissolved only at higher tempertures than the temperatures of the body or when in contact with specific substances and/or during a certain minimal time in order to control the dissolution of the capsule and the release of an additional substance, which has been inserted into the outer capsule, and/or in that as a material for the outer capsule and/or the inner capsule and the inner capsules respectively a mixture is used, which consists of solid paraffin and beeswax and/or in that as a material for at least one of the capsules and as a heavy substance waxes are used and/or paraffin with non-toxic substances, and/or in that the outer capsule is provided with an additional substance, e.g. a substance to be examined, either by insertion into the outer capsule in the form av a separate capsule (cargo capsule) or by a mixing with the chemically inert substance of at least one of the capsules and/or in that the inner capsule and the inner capsules respectively are designed and arranged in such a way, that they at least, when they are viewed from a certain angle individually and jointly respectively yield a non-circular or non-single point-shaped contrast picture.

3. A diagnostic means (11) used to carry out the diagnostic method according to claim 1 or 2, designed to indicate the migration of a medicament through the digestive apparatus and its resorption during this migration , with the

use of a negative MRI-contrast agent, e.g. Abdoscan, and a positive contrast and signal substance, introduced into one or several capsules (1) made of e.g. gelatin, **c h a r a c t e r i z e d in that** said one or several capsules (1) made of e.g. gelatin are arranged as inner capulses in a common outer capsule (2), which also contains a heavy substance, preferably barium sulphate, in such an amount, that the specific gravity of the filled outer capsule is higher than the specific gravity of the contents of the stomach in order to be able to sink through the contents of the stomach and to reach the small intestine without considerable time-delay.

4. A diagnostic means according to claim 3, **c h a r a c t e r i z e d in that** also iron oxide is introduced into the outer capsule (2) in order to form a satisfactorily contrasting negative near zone in relation to and around the inner capsule and the inner capsules (1) respectively.

5. A diagnostic means according to claim 3, **c h a r a c t e r i z e d in that** said positive contrast and signal substance is a natural or synthetic organic non-toxic substance, preferably a deep-sea fish oil.

6. A diagnostic means according to any of claims 3-5, **c h a r a c t e - r i z e d in that** the dissolution of the outer capsule (2) and possibly also the inner capsule or the inner capsules (1) respectively and one of the inner capsules respectively is designed to be delayed or counter-acted , at least during a certain predetermined time, by a coating, which is known per se, with beeswax and/or another non-toxic substance, which melts or is dissolved only at higher temperatures than the tempertures of the body or when contacted with specific substances and/or during a certain minimal time, the dissolution of the capsule (2) and the release respectively of an additional substance, carried along by the outer capsule (2), being controllable.

7. A diagnostic means according to claim 3, **c h a r a c t e r i z e d in that** the outer capsule (2) and/or the inner capsule and the inner capsules (1) respectively, consists of and/or contains a mixture of solid paraffin and barium sulphate.

8. A diagnostic means according to claim 3, **c h a r a c t e r i z e d in that** at least one of the capsules (1;2) contains said heavy substance, bound by or in waxes and/or paraffin.

9. A diagnostic means according to claim 3, **c h a r a c t e r i z e d in that** an additional substance , carried along by the outer capsule (2), e.g. a substance to be examined, either is inserted into the outer capsule (2) in the form of a separate capsule (cargo capsule) (6) or is mixed with the chemically inert substance, of which at least one of the capsules is made.

10. A diagnostic means according to any of claims 1-7, **c h a r a c t e - r i z e d in that** the inner capsule or the inner capsules (1) respectively are designed and arranged in such a way, that they, at least when they are viewed from a certain angle, individually or jointly respectively , yield a non-circular or a non-single point-shaped contrast picture.

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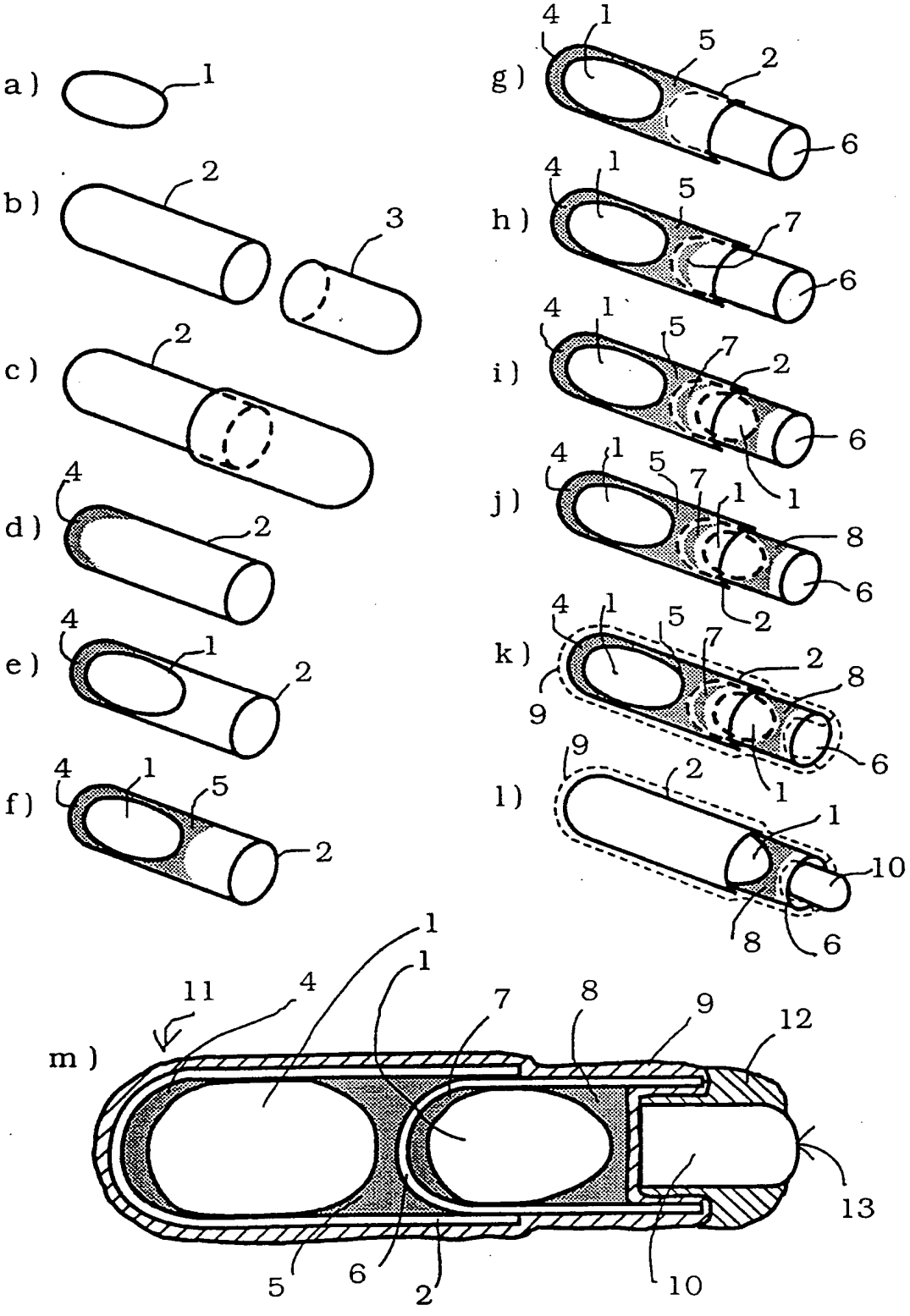

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 99/00889

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 49/00
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	DE 19745890 C1 (INSTITUT FÜR PHYSIKALISCHE HOCHTECHNOLOGIE E.V.), 25 March 1999 (25.03.99) --	1-10
A	US 5462053 A (RICHARD W. BRIGGS ET AL), 31 October 1995 (31.10.95) --	1-10
A	WO 9502831 A1 (COCKBAIN, JULIAN, RODERICK, MICHAELSONET AL), 26 January 1995 (26.01.95) --	1-10
A	WO 9811922 A2 (NYCOMED IMAGING ASET AL), 26 March 1998 (26.03.98) -- --------	1-10

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
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"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Date of the actual completion of the international search	Date of mailing of the international search report
21 Sept 1999	27-09-1999
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00889

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-2
because they relate to subject matter not required to be searched by this Authority, namely:

see next sheet

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE99/00889

Claims 1-2 relate to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1.(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

30/08/99

International application No.
PCT/SE 99/00889

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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